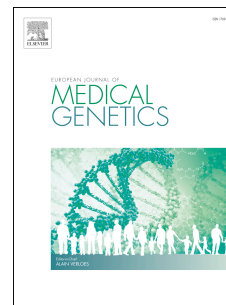


# Journal Pre-proof

Consensus recommendations on organization of care for individuals with Phelan-McDermid syndrome

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PII: S1769-7212(23)00053-8

DOI: <https://doi.org/10.1016/j.ejmg.2023.104747>

Reference: EJMG 104747

To appear in: *European Journal of Medical Genetics*

Received Date: 2 January 2023

Revised Date: 5 March 2023

Accepted Date: 18 March 2023

Please cite this article as: A.M. van Eeghen, D. Stemkens, José.Ramó. Fernández-Fructuoso, A. Maruani, K. Hadzsiev, ERN ITHACA Guideline Working Group, C.M.W. Gaasterland, M.J. Klein Haneveld, K. Vyshka, A. Hugon, A.M. van Eeghen, European Phelan-McDermid syndrome guideline consortium, I.D.C. van Balkom, Consensus recommendations on organization of care for individuals with Phelan-McDermid syndrome, *European Journal of Medical Genetics* (2023), doi: <https://doi.org/10.1016/j.ejmg.2023.104747>.

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**Title: Consensus recommendations on organization of care for individuals with Phelan-McDermid syndrome**

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**Abstract:**

The manifestations of Phelan-McDermid syndrome (PMS) are complex, warranting expert and multidisciplinary care in all life stages. In the present paper we propose consensus recommendations on the organization of care for individuals with PMS. We indicate that care should consider all life domains, which can be done within the framework of the International Classification of Functioning, Disability and Health (ICF). This framework assesses disability and functioning as the outcome of the individual's interactions with other factors. The different roles within care, such as performed by a centre of expertise, by regional health care providers and by a coordinating physician are addressed. A surveillance scheme and emergency card is provided and disciplines participating in a multidisciplinary team for PMS are described. Additionally, recommendations are provided for transition from paediatric to adult care. This care proposition may also be useful for individuals with other rare genetic neurodevelopmental disorders.

**Key words:**

Organization of care; centre of expertise; Phelan-McDermid syndrome; intellectual disability; guideline

## Introduction

Phelan-McDermid Syndrome (PMS) is caused by a deletion of 22q13.3 including the *SHANK3* gene or by a pathogenic variant in this gene and a diagnosis is based on the presence of molecularly confirmed *SHANK3* haploinsufficiency (Schön et al., 2023 this issue). Individuals are frequently affected by severe somatic and neuropsychiatric manifestations, including moderate-severe intellectual disability (ID), communication and language issues, epilepsy, mental health challenges, sensory deficits, and other organ dysfunction (Burdeus-Olavarrieta et al., 2023 this issue; Damstra et al. this issue, 2023; De Coo et al., 2023 this issue; Matuleviciene et al., 2013 this issue; San José Cáceres et al., 2023 this issue; van Balkom et al. this issue, 2023; Walinga et al., 2023 this issue). Due to lifelong care needs on multiple life domains, individuals with PMS present a challenging task for health care providers and care systems to provide optimal personalized care, taking both the characteristics of the genetic disorder as well as the individual into account. With improved medical care most individuals now reach adulthood, warranting personalized health care in all life stages including the transitional age and older adulthood. Increasingly, expert centres on specific genetic disorders like PMS are available, enabling health care providers such as clinical geneticists and paediatricians to identify, develop and improve treatment and care. The complex, multi-organ manifestations of PMS affect all life domains which can be considered within the framework of the International Classification of Functioning, Disability and Health (ICF)(WHO, 2001). This framework defines disability as the result of interactions between impairment, individual functioning and environmental factors (WHO, 2001). These interactions are evidenced by limitations in participation and activities, which determine the disability experience of the individual and sometimes necessitate lifelong care. We consider it likely that the care proposition described for PMS here may also be useful for individuals with other (rare) genetic neurodevelopmental disorders.

### *Care gaps*

Within European countries, there is great variability in content, organization, provision and access of care for individuals with PMS or other genetic neurodevelopmental disorders (NDDs), sometimes hampering implementation of personalized care and leading to unmet care needs.

After an often long and difficult diagnostic journey barriers to PMS-specific care may include lack of knowledge by local health care providers (HCPs), absence of PMS-experts, or lack of access to care, the latter is especially relevant for individuals from low socio-economic backgrounds or in adulthood (Wheeler et al., 2019).

Because caregivers often have more experience and expertise regarding the rare disorder, they are in the lead of care content and organization. Hence, they face a life-long challenge of negotiating health and social service systems for these individuals with ID who depend on others to understand and explain their needs (Kerr et al., 2003; Ouellette-Kuntz et al., 2005). It has been suggested, for example,

that family physicians may be unwilling to take on care for individuals with ID for a number of reasons, including inadequate training in the specific disorder (Wheeler et al., 2019) or in the field of ID, discomfort dealing with communicative and behavioural challenges common in individuals with ID, and problems of limited financial compensation for the extra time needed to work with such patients and their families (Hall et al., 2007). Transition from paediatric to adult care in itself has many challenges, crossing all dimensions of life. Individuals and caregivers need to find adult health care providers, ensure insurance coverage, and where possible, take ownership of their own health maintenance. In parallel, transition in various other spheres takes place, such as educational, vocational, financial, social, guardianship, and legal/decision-making responsibilities. Contextual issues such as parental stress, moving residence, and changing caregivers, can further complicate the transition process. Often, this results in loss to follow-up in health care (Both et al., 2018; Van Remmerden et al., 2020). Although various care models have been reported in the literature (Duis et al., 2019), there is no evidence that one model is more effective than others.

#### *European Guideline Infrastructure*

The European Reference Networks were established in 2017 to promote care and research collaborations on rare disorders in Europe. ERN ITHACA represents rare malformation syndromes with intellectual disability or other neurodevelopmental disorders. ERN ITHACA's mission is to synergize efforts to improve care for individuals with rare disorders in Europe by supporting working groups addressing issues of comorbidity, teaching, registries, guidelines, as well as ethical and legal considerations (Kline et al., 2018; Zollino et al., 2019). As it is not possible to provide separate guidelines for all of these >1500 disorders, so-called 'transdiagnostic guidelines' are also under development, focusing on frequently co-occurring comorbidity or care questions, as prioritized by stakeholders, such as challenging behaviour and transition from paediatric to adult care.

The present paper is part of a series of papers within the European Guideline on Phelan McDermid Syndrome and aims to describe and recommend a systematic approach to the organization of care for individuals with *SHANK3*-related Phelan-McDermid syndrome (OMIM#606232), defined as a deletion 22q13.3 including *SHANK3* or a pathogenic variant of *SHANK3*. A PMS-specific surveillance scheme is proposed. Recommendations on organization of care may also be applicable to *SHANK3*-unrelated PMS (Phelan et al., 2022) or other rare genetic neurodevelopmental disorders.

#### **Methods**

As part of the development of a European Guideline for Phelan-McDermid Syndrome (van Ravenswaaij-Arts et al., 2023 this issue), based on methodology of the AGREE II instrument (Brouwers et al., 2010), questions were formulated and literature was searched, selected and reviewed.

The following questions were defined by the PMS Consortium including patient representatives, as well as informed by caregiver concerns captured in a global survey (Landlust et al., 2023 this issue):

1. What is a European Reference Network?
2. What is a Centre of Expertise and where are PMS Centres of Expertise located?
3. What is the role of the PMS care team? Which disciplines are/should be involved in the multidisciplinary team for individuals with PMS?
4. What is the role of a coordinating physician, and who should this be in PMS?
5. How is transitional care arranged for individuals with PMS?
6. What is an individual care plan?
7. Is there a PMS registry?

#### *Literature review*

Literature on organisation of care and PMS was searched by including search terms for PMS and organization of care. Additionally, the Dutch guideline PMS (Federatie Medisch Specialisten 2018) was consulted, in which the literature was systematically searched and reviewed. These searches did not yield any PMS-specific results to address the above questions. Literature beyond PMS was also considered when relevant, for instance, studies addressing mental health in populations with intellectual disability. Hence, a supplementary exploratory search of literature was performed in PubMed, identifying recommendations for organization of care, using search terms 'organization of care' or 'transition of care', 'care recommendations' and 'rare genetic syndrome' or 'intellectual disability' over 2000-2020, striving to include different life phases, medical conditions and divergent psychosocial profiles, yielding 18 publications (Adeniyi & Adeniyi, 2020; Auvin et al., 2019; Both et al., 2018; Doody et al., 2019; Duis et al., 2019; Kerr et al., 2014; Kim et al., 2011; Kline et al., 2018; McAllister et al., 2018; Minnes et al., 2009; Northrup et al., 2021; Peters et al., 2022; Stuart et al., 2021; Santoro et al., 2021; Seth van Zant et al., 2021; Van den Driessen Mareeuw et al., 2020; Van Remmerden et al., 2020; Zollino et al., 2019). The EUCERD Recommendations on Quality Criteria for Centres of expertise for Rare Diseases (EUCERD 2011), the RARE 2030 recommendations (Kole & Hedley, 2021), and NICE Guideline Transition from children's to adult's services or young people using health or social care services (National Institute for Health and Care Excellence 2016) were reviewed. Designated to cover the topic of organization of care for individuals with PMS was a working group consisting of one physician for the intellectually disabled (AvE), two patient representatives (DS; JF-F), and two psychiatrists (AM, IvB).

#### *Survey results*

A recent global parental survey on PMS (Landlust et al., 2023 this issue) revealed caregiver experiences around the organization of care for an individual with PMS.

Of 583 respondents, 171 individuals (29%) received care at a local or regional hospital, 26% at an academic or university hospital, 9% at a PMS-expert centre and 22 individuals (4%) received care at a centre of expertise for rare syndromes. In the same survey 68.1% of parents indicated levels of extreme stress and worry about the transition to adult care of their loved one with PMS. Lastly, a need for a guideline was expressed, which is addressed in this special issue.

#### *Formulation of recommendations*

Results of patient surveys and literature were extensively discussed during working group and PMS consortium meetings, and categorized according to the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001) to provide a comprehensive interpretation. Conclusions and proposed recommendations were finalized at a consortium consensus meeting, where recommendations were rephrased until consensus was met (Tables 1 and 2).

Separate work (KH) resulting in a surveillance scheme for this syndrome was included in this paper (Table 3).

#### **Overview of information**

Apart from the current European guideline and consensus recommendations on diagnostic assessments, treatment and follow-up, there is no PMS specific literature available on organization of care. Selected literature, a global survey on PMS caregiver experiences, workgroup and consensus meetings served as a basis for the considerations below.

#### *European Reference Networks (ERNs) and ERN-ITHACA*

Centres of expertise should be involved in European Reference Networks (ERNs) and cross-border care when appropriate and possible (EUCERD 2011). ERNs are virtual networks involving healthcare providers and patient representatives across Europe established by the Directive on cross-border healthcare (Tumiene et al., 2021). They aim to facilitate discussion on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources.

ERN-ITHACA is one of the 24 already established ERNs within a European context and identifies as a patient centred network which meets the needs of those with rare congenital malformations and syndromes with intellectual disability and other neurodevelopmental disorders. More than 1500 rare disorders of both genetic and non-genetic origin are covered by ITHACA, among which PMS. For more information on establishing a CE for PMS, contact ERN-ITHACA.



### *Centres of Expertise (CE)*

Centres of Expertise (CE) are recognized expert organisations for the management and care of rare disease (RD) patients. Each Centre of Expertise is specialised in a single Rare Disease or group of Rare Diseases and shares the mission of providing Rare Disease patients with the highest standards of care to deliver timely diagnosis, appropriate treatments, and follow up (EUCERD 2011). A CE is responsible for the management and general coordination of the integrated care chain. Integrated care is defined as care in which different care providers coordinate their activities as much as possible so that the individual receives care on all life domains, within a CE where necessary, or locally where possible (Figure 1). The coordinator of the centre of expertise is usually a medical specialist and often a member of the care team. CEs also contribute to research efforts through participation in both data collection for clinical research and in clinical trials.

[please insert Figure 1 close to the paragraph above]

Figure 1. Proposed care network of an individual with PMS, or other genetic neurodevelopmental disorder.



### *PMS Centre of Expertise*

A list of European Centres of Expertise in the field of PMS can be found on the Orphanet website (<https://www.orpha.net/consor4.01/www/cgi-bin/Clinics.php>). In practice, the care for PMS benefits from collaboration between the centre of expertise and a regional care team (shared care).

In many countries, a CE specifically for PMS is not available. In these cases, advice can be sought at centres affiliated with ERN ITHACA (<https://ern-ithaca.eu/>). Alternatively, this can be sought among local specialists providing care to individuals with ID, such as paediatricians or clinical geneticists.

Patient organisations are often aware of expertise and can facilitate referrals [[link to national patient organisations and contact info](#)]. Additionally, often peer support, informational activities and other support is organized by patient organisations.

### *Multidisciplinary expert team for individuals with PMS*

The composition of a multidisciplinary expert team for individuals with PMS will depend on which professionals deliver the required care in that country. The multidisciplinary team may consist of a paediatrician, clinical geneticist, (child and youth) psychiatrist, (child) neurologist, intellectual disability physician, (neuro-)psychologist, general practitioner, rehabilitation doctor, public health care professionals, behavioural therapist, and paramedics like a speech therapist.

The surveillance scheme (Table 3) [please insert in lay-out over two pages where appropriate and fitting] provides an overview of points for attention in the follow-up of individuals with PMS. Additionally, an emergency card is provided (Suppl. Table S1). Both can be adapted on an individual level as well as to the local and national circumstances.

Depending on the care needs of the individual with PMS, the expert team can be supplemented with other specialists (ENT doctor, ophthalmologist, vascular surgeon/dermatologist, family support or other care).

Optimal communication and information transfer between care providers in the multidisciplinary teams is essential in the care for individuals with PMS. The coordinating physician plays a central role in this.

### *Regional care team*

The regional care team is the local or regional team around the individual with PMS and responsible for direct care and guidance in coordination with the Centre of Expertise (CE). In addition to reporting and periodically sharing medical data/findings, the regional care team regularly consults with the Centre of Expertise on the content of the care offered, e.g., local versus CE monitoring, and in case of

complex manifestations or care needs. The primary care physician is an important part of this care team. Depending on the individual's care needs other disciplines may be included, for example a psychologist, buddy, social worker, neurologist, internist, psychiatrist, ID physician, nurse, and paramedical specialities.

In some countries only a regional care team may be available as there may not be a national Centre of Expertise; sometimes a national Centre of Expertise will also provide regional care.

Whether a patient is primarily treated and/or monitored in a Centre of Expertise or by a regional care team depends on several factors. The goal is to provide as much care as possible nearby and only travel further when absolutely necessary.

### *Coordinating physician*

Each individual with PMS has one coordinating physician, sometimes in the Centre of Expertise but usually within the regional care team where the person with PMS is being treated/monitored.

Preferably, the coordinating physician is an easily accessible medical specialist "close to home".

Depending on the stage of life and personal circumstances of the individual with PMS, care may be organized in an academic, top clinical or peripheral hospital, clinic or an organisation for individuals with ID.

At diagnosis the coordinating physician considers, as described in the ICF-framework, factors on all life domains that may influence physical and mental health and functioning of the individuals with PMS leading to a comprehensive diagnostic formulation (van Balkom et al., 2023 this issue). With a first diagnosis in childhood, the coordinating physician is most often the paediatrician. Depending on the individual's care needs, the role of coordinating physician may subsequently be transferred to another medical specialty (e.g. rehabilitation specialist, internal medicine specialist, neurologist, intellectual disability physician, primary care physician).

The coordinating physician:

- Maintains a medical overview, provides and maintains direction, monitors and coordinates the total (lifelong) multidisciplinary care of a person with PMS, including follow-up, monitoring and the transition from child to adult care (when the role of coordinating physician can be transferred to another medical specialist or primary health care provider).
- Is the point of contact for (carers of) the individual with PMS for questions about care.
- Is the point of contact for experts of the PMS Centre of Expertise.

- Draws up the individual care plan together with (the caregivers of) the person with PMS (with possible consultation of the multidisciplinary treatment team and the Centre of Expertise) and supervises its implementation and appropriateness.
- Supports the self-management of (the carers of) the individual with PMS.
- Has access to recent scientific developments and new treatment methods in PMS (possibly via the Centre of Expertise).

All those involved (representatives and care providers of a person with PMS) know who the coordinating physician is. This information is recorded in the individual care plan (ICP).

### *Transition of care*

Individuals are often lost to, or decline, follow up as they leave paediatric care, and it is largely unclear how, where, and why adults with PMS receive health care later in life.

Transition is the deliberate systematic transfer of adolescents and young adults with a chronic condition from a child-oriented care system to a care system aimed at adults (Blum et al., 1993). In the NICE guideline (National Institute for Health and Care Excellence 2016) for transition of care, the following is recommended:

- Awareness of risks of poor transitional outcomes and/or loss to follow-up
- Timely addressing of milestones to be achieved during the transitional age;
- Timely reporting of the moment of transfer, at least from the age of 14;
- Timely involving (multidisciplinary) care team for adults;
- Good transfer of written documentation including detailed patient history;
- At least one joint consultation with a multidisciplinary team (for transfer between paediatric and adult specialists), this can be organized in-person or digitally (NICE 2016).

Risk factors for poor transitional outcomes and / or loss to follow-up may include poor socio-economic circumstances, moving residence, lack of appropriate daytime activities)

Continuity of care for individuals with rare genetic syndromes is inherently more complex, as more health care providers are needed, in specialist and general hospitals, and in primary care. This life phase is stressful for the individual with PMS as well as for caregivers, with changing needs and care on all life domains (Both et al., 2018; Van Remmerden et al., 2020). Especially psychosocial issues such as social isolation and mood disorders may arise and can be difficult to address. Also, special attention for guaranteeing optimal autonomy of the individual with intellectual disability is warranted, while simultaneously organizing support where necessary.

The coordinating physician organizes the transition of care, if necessary in consultation with the Centre of Expertise. The Centre of Expertise ensures continuation of PMS specific care in adulthood.

The coordinating physician during childhood and the future coordinating physician for adult care both agree to the transfer and inform the Centre of Expertise and the involved expert team members. National guidelines may also be available that are more specific to local organisation of care and an ERN ITHACA guideline on transitional care is under development.

#### *Individual Care Plan (ICP)*

An individual care plan (ICP) is a dynamic set of agreements between the patient and the care provider(s) about care and self-management. These agreements are based on the individual goals, needs and situation of the patient. They come about through joint decision-making (CPZ, 2012). The ICP is a flexible document that follows the problems and needs of a patient: it is simple and short, if possible, but complex and extensive if necessary. The follow up scheme (Table 3) can be used as template and the emergency card (S Table 1) can be included.

The coordinating physician can draw up the ICP in collaboration with the (caretakers of the) person with PMS. At diagnosis, the ICP contains, at minimum, the contact information of the coordinating physician and the initial monitoring and/or treatment plan.

#### *PMS Registry*

A European registry for PMS does not exist yet. Such a registry would be important for clinical research, healthcare planning and for the improvement of clinical care.

ILIAD (an International Library of Intellectual disability and Anomalies of Development) is an interoperable registry dedicated to rare diseases within the scope of and under the supervision of the ERN-ITHACA network. ILIAD targets patients with developmental anomalies (dysmorphic/multiple congenital anomalies syndromes and/or neurodevelopmental disorders [<https://eu-rd-platform.jrc.ec.europa.eu/erdridor/register/5009>]). Currently, the European PMS consortium is working on an ILIAD-based sub registry that collects more disease-specific information on PMS individuals known to the consortium members, representing most European countries, in order to support research.

The GENIDA project is a participatory international database to collect medically relevant information on genetic forms of Intellectual Disability / Autism Spectrum Disorder, for families and professionals. This database encourages the development of clinical research in the field of rare diseases, as well as improve patient care, and healthcare planning [<https://genida.unistra.fr/>].

## ERN ITHACA Guideline Working Group

Table 3. Surveillance scheme summarizing recommendations for follow-up of individuals with *SHANK3*-related Phelan-McDermid syndrome (PMS).

		AT DIAGNOSIS	0-2 YEARS	2-12 YEARS	12-16 YEARS	>16 YEARS
GENETICS	Genetic counselling of relatives to discuss: - phenotype PMS - Recurrence risk: FISH and karyotyping (also to exclude ring 22) - reproductive options - family support groups					
	Referral to (PMS) centre of expertise (CE) for follow-up, general updates on PMS, participation in research, collecting data and providing (new) information to families.		Yearly	Every 2 years	Every 2 to 3 years	Every 3 to 5 years
MENTAL HEALTH	Cognition and development	Comprehensive evaluation. Baseline measurement of functioning level.	Assessment of development. Initiate early intervention.	Assessment and follow-up of development. Continue intervention.	Assessment and follow-up of development. Continue intervention.	
	Adaptive and sensory functioning	Comprehensive evaluation. Baseline measurement of functioning level.	Assessment of development. Initiate early intervention.	Assessment and follow-up of development. Continue intervention.	Assessment and follow-up of development. Continue intervention.	
	Psychiatric and behavioural status	Baseline measurement.	Monitor changes in skill level. Monitor changes in behaviour. If symptom onset, rule out medical issues.	Monitor changes in skill level. Monitor changes in behaviour. If symptom onset, rule out medical issues. Consider comorbid mental health problems.	Monitor changes in skill level. Monitor changes in behaviour. If symptom onset, rule out medical issues. Consider comorbid mental health problems.	If symptom onset, rule out medical issues. Consider comorbid mental health problems.
COMMUNICATION, SPEECH AND LANGUAGE	Difficulties with communication, language and speech	Refer to an audiology specialist. Assess and initiate intervention by (preverbal) speech therapist.	Follow up of hearing/conduction problems*. Assess and initiate intervention by (preverbal) speech therapist.	Follow up of hearing/conduction problems*. Consider support with augmentative/alternative communication. (Preverbal) speech therapy at home/school.	Follow up of hearing/conduction problems*. Continue support with augmentative/alternative communication. (Preverbal) speech therapy at home/school.	Follow up of hearing/conduction problems*. Continue support with augmentative/alternative communication.
SLEEP DISORDER	Sleep disorders/problems at all ages: - Check somatic causes - Check mental health issues - Use structured questionnaires - Check parental stress	Check for sleep problems & parental stress.	Sleep clinic or sleep specialist.	Sleep clinic or sleep specialist.	Sleep clinic or sleep specialist.	Sleep clinic or sleep specialist. Check for: - Apnoea - Parasomnias

EYE AND VISION	Strabismus, refraction errors and cortical visual impairment	Refer to eye specialist.	Refer to eye specialist if indicated. Check vision*.	Refer to eye specialist if indicated. Check vision*.	Refer to eye specialist if indicated. Check vision*.	Refer to eye specialist if indicated. Check vision*.
EAR AND HEARING	Recurrent middle ear infections, hearing problems	Refer to an ENT specialist: audiometry and tympanometry.	Refer to ENT specialist if indicated. Check hearing*.	Refer to ENT specialist if indicated. Check hearing*.	Refer to ENT specialist if indicated. Check hearing*.	Refer to ENT specialist if indicated. Check hearing*.
	Delayed response to verbal and auditory clues	Keep in mind in communication.	Keep in mind in communication.	Keep in mind in communication.	Keep in mind in communication.	Keep in mind in communication.
ALTERED SENSORY FUNCTIONING	Reduced pain response	Be extra alert for (underlying) somatic problems.	Be extra alert for (underlying) somatic problems.	Be extra alert for (underlying) somatic problems.	Be extra alert for (underlying) somatic problems.	Be extra alert for (underlying) somatic problems.
	Heat regulation problem, decreased perspiration	Be aware of overheating.	Be aware of overheating.	Be aware of overheating.	Be aware of overheating.	Be aware of overheating.
	Hypersensitivity to touch	Take into account while examining.	Take into account while examining.	Take into account while examining.	Take into account while examining.	Take into account while examining.
	Altered sensory functioning	Refer to a sensory integration specialist.				
GASTROINTESTINAL	Feeding problems (reduced sucking reflex, chewing)		Speech therapy.	Speech therapy.		
	Gastroesophageal reflux	If needed: Dietary advice Proton pump inhibitors	Dietary advice Proton pump inhibitors	Dietary advice Proton pump inhibitors	Dietary advice Proton pump inhibitors	Dietary advice Proton pump inhibitors
	Cyclic vomiting		Refer to paediatrician to exclude somatic cause	Refer to paediatrician to exclude somatic cause		
	Overweight: nutritional and exercise advice (dietician, physiotherapist)					
	Constipation	If needed: Dietary advice laxatives	Dietary advice laxatives	Dietary advice laxatives	Dietary advice laxatives	Dietary advice laxatives Consider testing for megacolon.
HEART AND LUNGS	Cardiac ultrasound					
	Congenital abnormalities (including TI- tricuspid insufficiency, ASD- atrial septal defect, PDB- Persistent ductus Botalli)	Consult cardiology: ECG, US (<2 years) if indicated.				
	Recurrent upper airway infections					
NEUROLOGY	Brain structural abnormalities	Low-threshold MRI of the brain at indication (paediatric)neurologist.				
	Hypotonia: poor head control, feeding problems, fatigue, insufficient movement.		Paediatric physiotherapist, occupational therapy, speech therapy.	Paediatric physiotherapist, occupational therapy, speech therapy.	Advise sports, possibly under the supervision of a physiotherapist.	Advise sports, possibly under the supervision of a physiotherapist.
	Delayed motor development, motor dyspraxia, hyperlax joints		Paediatric rehabilitation doctor, child physiotherapist, occupational therapy.	Paediatric rehabilitation doctor, child physiotherapist, occupational therapy.		
	Epilepsy, frequent febrile seizures		Paediatric neurologist and EEG at indication.	Paediatric neurologist and EEG at indication.	Paediatric neurologist and EEG at indication.	Paediatric neurologist and EEG at indication.
END OCRI NE	Height					



	Hypothyroidism	TSH	Investigate only if behavioural changes consistent with thyroid dysregulation.	Investigate only if behavioural changes consistent with thyroid dysregulation.	Investigate only if behavioural changes consistent with thyroid dysregulation.	Investigate only if behavioural changes consistent with thyroid dysregulation.
RENAL UROGENITAL	Congenital abnormalities: vesicoureteral reflux, cystic or dysplastic kidneys, or hydronephrosis	Perform US of kidneys/urinary tract at least once				
	Recurrent urinary tract infections					Exclude underlying problems and consider prophylaxis.
	Birth control and family planning					
SKIN AND LYMPH	Dysplastic, thin toenails that frequently become ingrown					
	Primary lymphedema, prevalence increasing with age				Consider referral to a CE for lymphedema.	Consider referral to a CE for lymphedema.
	Be alert to overheating and/or decreased perspiration					
TUMOURS (in ring chromosome 22)	Monitoring for potential NF2-tumours, including eye and neurological examinations				Every 1 to 2 years.	Every 1 to 2 years.
	Baseline cerebral/spinal imaging (MRI)					
	MRI in case of symptoms of lethargy, unilateral weakness and/or ataxia and hearing loss					
ANAESTHESIA /MRI	Assistance with preparing the individual for procedures like an MRI or anaesthesia should be discussed with parents.					
	Close monitoring of anaesthetic depth <sup>#</sup>					

General note: The coloured boxes in the scheme indicate when a specific check is recommended. The columns contain items that are advised at least once when making the diagnosis. For background information and further details see the relevant papers in this special issue, listed in the references. For prevalence of the clinical features see Schön et al (2023 this issue). All follow-up appointments may be more often when indicated.

ECG: electrocardiogram; EEG: electroencephalogram; US: ultrasound

\* According to national guidelines

<sup>#</sup> Close monitoring of anaesthetic depth seems useful because there may exist an increased sensitivity to anaesthetics, based on hypersensitivity for isoflurane in *Shank3*-haploinsufficient mice (Li et al., 2017). However, to date there is no clear hint of anaesthesia complications in humans with PMS.

## Recommendations

During working group meetings, conclusions and recommendations were formulated based on the selected literature and input from the global parental survey (Landlust et al., 2023 this issue)(Table 1 + 2) [please insert table 1 and 2 together where fitting, preferable at the end of the document before the final conclusion]. A ‘per patient approach’ of care for individuals with PMS should be organized within the framework of the ICF, which considers all life domains to assess the individual’s functioning and care needs. Multidisciplinary collaborations are important to ensure optimal relevance and alignment with the individual’s care needs and prevent loss to follow up. P4 (predictive, preventative, participatory, personalized) (Hood 2011) medicine can be used as an approach to empower clinicians to implement local and national care paths together with patient representatives, optimally integrating these with research, education, and guidelines (Van Eeghen 2022). Ethical issues to consider include



ensuring access to genetic diagnostics and personalized care for those residing in lower income countries, as well as for adults with PMS and/or ID. With increased life expectancy of individuals with NDDs (Coppus 2013; Stepien 2021), the largest PMS population is now likely comprised of adults, many of which have not (yet) been accurately assessed or diagnosed and may have unmet care needs due to lack of access to appropriate care.

#### *Centres of Expertise*

Expert, PMS-specific care would ideally be available in a full facility academic clinic, where all involved research and clinical disciplines can interact to provide holistic care to the patient and family. It is recommended that care is provided in a 'transmural' fashion, within academic multidisciplinary expert centres when necessary and by a local care team where possible, to minimize burden on the individual patient and caregivers. In this way, patient-friendly transmural care networks can be established, preferably supported by shared electronic patient records. Accessible information on diagnostics and therapies will lower the threshold for health care providers and patients alike. Development of patient-centred outcome measures (PCOMs), where needed specific for PMS, will help identify relevant clinical questions and monitor care needs and quality of life.

When PMS expert centres function as knowledge centres of clinical practice, not only can they provide (virtual) consultations, they can assume regional, national, and even European and international teaching roles with the possibility to actively reach out to health care providers, individuals with PMS and their caregivers.

\*For more information on establishing a centre of expertise, contact ERN ITHACA.

#### *Continuity of care*

Optimally, the local coordinating HCP has the closest relationship with the patient, and communicates regularly with the PMS expert centre as well as with other regional HCPs. During the transitional age phase, this appointed person organizes transfer to adult health care providers, according to NICE Guidelines (National Institute for Health and Care Excellence 2016), supported by the PMS expert centre and regional HCPs. The framework of the ICF (WHO, 2001) can be helpful for assessing functioning and identifying care needs to organize the content and domains of care for individuals with PMS.

Next to medical and psychological documentation, periodic Individualized Education Plans (IEPs) are especially useful for recording life events, functioning and personal goals over time.

#### *Registries*

Registries, preferably patient-owned, are necessary at local, regional and (inter)national levels to improve knowledge, enable longitudinal monitoring of features on all life domains, as well as disseminate evidence- and practice-based knowledge to improve organization of care. Hence, individuals and their support networks will have information on the course of their individual functioning, and can evaluate severity of comorbidity or effectiveness of interventions retro- and prospectively. Such life-long monitoring including digital technologies can prevent that the patient with PMD, and all patients with ID, will be 'known well by no one' in adulthood (Camfield & Camfield, 2011).

### **Conclusion**

Opportunities to improve care and treatment of complex NDDs such as PMS are emerging at a steady rate. As information and knowledge increase, it is clear that patients and their families deserve and demand a new paradigm in care. We suggest that care should consider all life domains using the framework of ICF to assess disability and to understand that functioning is the result of the individual's interactions with other factors. Services that encompass the ICF-model will assess functioning within the larger context of the positive and negative relationships between impairment, individual functioning and environmental factors such as family (WHO, 2001) and better clarify the individual's care needs. Exploring these relationships within the ICF-model will inform interventions, further improve understanding of the individual's strengths and weaknesses, and add to the individual's and family's quality of life.

As a starting point, the current consensus on how to address care needs in individuals with PMS will improve multidisciplinary, lifelong personalized care for this complex and vulnerable patient population. Together, patients and their support networks, health care professionals and researchers can unite forces and accelerate personalized medicine for individuals with PMS and other NDDs.

### **Acknowledgements:**

This project has been supported by the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA).

#### **Funding:**

ERN-ITHACA is partly co-funded by the Health Programme of the European Union.

Funding was also obtained from the European Union's Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575.

**Table 1.** Conclusions as agreed upon by the European Phelan-McDermid syndrome consortium

Centres of Expertise (CEs) are nationally appointed expert organisations for the management and care of rare disease patients. CEs should be involved in European Reference Networks (ERNs).
The <u>regional care team</u> is the local/regional team around the person with PMS that is responsible for direct care and guidance in coordination with the centre of expertise.
The <u>multidisciplinary expert team</u> includes the health care providers associated with CEs.
The composition of the regional care team and multidisciplinary expert team will depend on which professionals deliver the required care in that country. The surveillance scheme (Table 3) provides an overview of points for attention in the follow-up of individuals with PMS. This scheme needs to be adapted on an individual level as well as to the local and national circumstances.
The coordinating physician for an individual with PMS can vary per life stage and is sometimes part of? the centre of expertise, but usually within the regional care team. It is often a medical specialist such as a paediatrician, internal medicine specialist, primary care physician or intellectual disability physician.
The coordinating physician coordinates the transfer to adult care, if necessary, in consultation with the centre of expertise and care team.
An individual care plan (ICP) is a dynamic set of agreements between the patient and the care provider (s) about care and self-management.
A European registry for PMS does not exist yet.

Table 2. Consensus recommendations as agreed upon by the European Phelan-McDermid syndrome consortium

Every person with PMS should receive PMS-specific care by a dedicated expert team, preferably in a centre of expertise.
A coordinating professional should initiate and monitor the multidisciplinary care for a person with PMS. The multidisciplinary team should be established based on the surveillance scheme (Table 3).
For every person with PMS, specific care needs and the responsible professionals should be recorded in the medical records and the individual care plan, if available.
For every teenager with PMS, the transition from paediatric to adult care is timely initiated and monitored by the coordinating paediatric professional. Coordinating should be transferred to a professional in adult care. This should be recorded in the medical records and individual care plan.

Caregivers of individuals with PMS should be informed about the patient registry of the PMS when established.

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- European Reference Network (ERN) ITHACA (<https://ern-ithaca.eu/>)
- Orphanet link to patient organisations and contact info: [https://www.orpha.net/consor/cgi-bin/SupportGroup\\_Search\\_Simple.php?lng=NL&LnkId=10630&Typ=Pat&fdp=y&from=rightMenu](https://www.orpha.net/consor/cgi-bin/SupportGroup_Search_Simple.php?lng=NL&LnkId=10630&Typ=Pat&fdp=y&from=rightMenu)
- Orphanet list of European Centres of Expertise: [https://www.orpha.net/consor4.01/www/cgi-bin/Clinics\\_Search\\_Simple.php?lng=FR&LnkId=10630&Typ=Pat&CnsGen=n&fdp=y&from=rightMenu](https://www.orpha.net/consor4.01/www/cgi-bin/Clinics_Search_Simple.php?lng=FR&LnkId=10630&Typ=Pat&CnsGen=n&fdp=y&from=rightMenu)
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